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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,532	05/25/2001	Beverly L. Davidson	PP16065.003	4232

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,532	DAVIDSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,11-14 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,11-14 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed September 30, 2003 has been entered. Claims 1, 5-7, and 19-21 have been amended. Claims 4, 8-10, 15-18, and 22 have been cancelled.

Accordingly, Claims 1-3, 5-7, 11-14, and 19-21 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 11, and 12 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-7 of the Office Action of Paper No. 10 (mailed 4/1/03), and for further reasons as discussed herein, because the specification, while being enabling for *in vitro* applications of the method, does not reasonably provide enablement for *in vivo* applications of the method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for transducing a cerebellar neuron. The specificaton contemplates using the claimed method *in vivo* for gene therapy applications. The claims encompass both *in vitro* and *in vivo* applications. The specification contemplates using the claimed invention therapeutically to treat a wide variety of CNS disorders as set forth at page 6, line 21 through page 7, line 17. Thus, the only utility asserted for *in vivo* applications of the claimed methods is to produce a

therapeutic effect, but the specification fails to adequately teach how to use the claimed methods therapeutically. It is well-established that the specification must teach how to use the claimed method over the full scope. With regard to *in vivo* applications, enablement is evaluated for the sole asserted utility. The only *in vivo* use asserted is for gene therapy.

At page 7 of the response, Applicants argue that the Examiner is impermissibly importing an *in vivo* therapeutic use limitation from the specification into the method of transducing claims where such a limitation is not recited. Applicants further state that the Examiner implies that the only asserted utility for transducing cerebellar cells is *in vivo* gene therapy methods and that contrary to this implication the specification explains that the methods are useful for transducing cells *in vitro* as well as *in vivo*. However, the Examiner has already explicitly indicated that the specification **is enabling for *in vitro* applications**. Contrary to Applicants' assertion, the Examiner noted that "[t]he claims cover both *in vitro* and *in vivo* applications. . . . the only utility asserted for *in vivo* applications of the claimed methods is to produce a therapeutic effect, but the specification fails to adequately teach how to use the claimed methods therapeutically." (page 3, paragraph 3 of the previous Office Action). It is well established that the specification must teach how to use the claimed method over the full scope.

At page 7, paragraph 3 of the response, Applicants assert that the specification fully enables use of the claimed methods for the purpose of *in vivo* gene therapy. Applicants argue that the PTO has not met the initial burden for showing reason to doubt the objective truth of the statements of the specification which must be relied on for enabling support. While the PTO bears the initial burden of providing reasons for doubting the objective truth of the statements made by Applicants as to the scope of enablement, when the PTO meets this burden, the burden shifts to applicant to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In the instant

case, the Examiner has cited eight references discussing the state of the art with regard to gene therapy and has further provided an analysis of the *Wands* factors as they relate to the instantly claimed invention.

At page 8 of the response, Applicants point out that the specification exemplifies *in vivo* administration of a lentiviral vector containing β-galactosidase as the protein of interest and demonstrates the transduction of Purkinje cells. Applicants further point out that the specification provides an extensive list of genes encoding a wide variety of polypeptides, proteins or enzymes that, when expressed, one of skill in the art would expect to prevent or alleviate the effects of a particular cerebellar or CNS disorder. Applicants specifically point to the suggestion to express tyrosine hydroxylase to alleviate the symptoms of Parkinson's disease. However, no support is provided for Applicants' assertion that "one of skill in the art would expect [the expression of these genes] to prevent or alleviate the effects of a particular cerebellar or CNS disorder." On the contrary, while the art recognizes the association of particular genes with particular diseases, the references cited by the Examiner demonstrate that the skilled artisan recognized that much more than routine experimentation was required to take a gene delivery method and develop a gene therapy protocol. At the time of the invention, the skilled artisan recognized that the art was highly unpredictable and undue experimentation was required to develop therapeutic protocols.

At page 8, paragraph 5, Applicants argue that the reference of Orkin and Motulsky was published five years before the priority date of the instant application and that the field of gene therapy advanced a great deal during that period of time. However, Applicants have not provided any rebuttal evidence showing that the state of the art advanced so rapidly that gene therapy could be accomplished by routine experimentation in May 2000 upon provision of a gene delivery method. Such is not the case, as evidenced by Rubanyi et al. (2001), published after the effective filing date of the instant application. Rubanyi (2001) teaches that the problems described by Orkin and Motulsky (1995), Friedmann (1997), Verma et al. (1997), Miller et al. (1995), Deonarain et al. (1998), Crystal et al. (1995), and Ross et al.

(1996) remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far ..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pp. 116-125).

At page 8, paragraph 6 of the response, Applicants argue that targeting of specific tissues is accomplished by use of the claimed method because "Applicants have demonstrated that the transduction methods of the present invention are capable of specifically transducing cerebellar neurons, such as Purkinje cells." However, it is unclear what Applicants are attempting to argue here because it is well known that lentiviral vectors transduce a variety of different neuronal cell types as well as other cell types. Therefore, it is not accurate to say that the method of the invention **specifically** transduces **cerebellar** neurons.

At page 9, paragraph 2 of the response, Applicants dismiss the teachings of Verma et al. because the "present invention exemplifies the successful expression of a protein of interest" in cerebellar neurons. Applicants conclude that the specification teaches the use of regulatory elements effective in cerebellar neurons. However, what is missing from the specification is the essential teaching of achieving a useful *in vivo* effect. The specification explicitly asserts that a **therapeutic** effect can be achieved. However, β-galactosidase expression has not been used therapeutically and one of skill in the art would not expect β-galactosidase expression to have a therapeutic effect. The specification must teach how to use the claimed invention *in vivo*. Given that the only use asserted in the specification for *in vivo* transduction of cerebellar neurons is for production of a therapeutic effect, the specification must enable this use.

At page 9, paragraph 3 of the response, Applicants argue that the efficiency of gene transfer within the injected lobule was nearly 100%. However, for the reasons discussed above, given that one of skill in the art would not accept that β-galactosidase can be used therapeutically in Purkinje cells, provision of a method for *in vivo* gene delivery is not equivalent to providing a gene therapy protocol. It is well established in our law that the claimed invention must be enabled over the full scope at the time of filing.

At page 10, paragraph 3 of the response, Applicants cite Brooks et al. (2002) for describing the use of a lentiviral vector to correct a central nervous system disorder. Since this reference is post-filing art, one of skill in the art would not have had the benefit of the teachings of Brooks et al. (2002) and therefore would not have been able to develop a therapeutic protocol for the treatment of lysosomal storage disease without undue experimentation. The instant specification does not provide specific guidance for expressing β-glucuronidase at therapeutic levels in the striatum, cerebral cortex, or hippocampus as described by Brooks et al. Rather the instant method is directed to providing expression within cerebellar neurons. Thus, Applicants arguments are not commensurate in scope with the scope of the claims.

Given the lack of applicable *in vivo* working examples, the limited guidance provided in the specification, the broad scope of the claims, and the unpredictability for achieving a therapeutic effect upon *in vivo* gene transfer, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a vertebrate subject for therapeutic benefit.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

Claims 6, 7, 13, 14, and 19-21 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on page 7 of the Office Action of Paper No. 10 (mailed 4/1/03), as containing subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The claims are directed to a method for transducing a cerebellar neuron *in vivo* or *ex vivo*, a method of treating or preventing cerebellar neuronal degeneration, and a method of treating or preventing a central nervous system disorder. The claims are exclusively directed to *in vivo* methods and *ex vivo* protocols that require administration of a neuron to a subject. These claims do not encompass *in vitro* applications.

For the reasons discussed above and reasons of record, the specification fails to provide an enabling disclosure for therapeutic protocols.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19 and 20 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 20 are indefinite in their recitation of "treating or preventing cerebellar degeneration in the subject" because the preamble states that the claim is directed to "treating or preventing cerebellar neuronal degeneration" and thus the conclusory statement is broader in scope than the scope of the preamble. The term "cerebellar degeneration" is construed to cover degeneration of any cell type or any region within the cerebellum and therefore covers more than "cerebellar neuronal degeneration."

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (703) 305-3482.

Art Unit 1632 will be moving to the new USPTO headquarters on January 13, 2004. After that date, Examiner Falk can be reached at (571) 272-0728 and Examiner Reynolds can be reached at (571) 272-0734.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER